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Neuroscience and Biobehavioral Reviews 29 (2005) 67–81
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
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Review

Social factors and individual vulnerability to chronic stress exposure

Alessandro Bartolomucci[a,b,*], Paola Palanza[a], Paola Sacerdote[c], Alberto E. Panerai[c], Andrea Sgoifo[a], Robert Dantzer[d], Stefano Parmigiani[a]

[a]*Dipartimento di Biologia Evolutiva e Funzionale, Università di Parma, Parma, Italy*
[b]*Instituto di Psicologia, Università di Milano, Milano, Italy*
[c]*Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica, Università di Milano, Milano, Italy*
[d]*Laboratoire de Neurobiologie intégrative FRE CNRS, UMR INRA-Université Victor Ségalen Institut François Magendie, Bordeaux, France*

Abstract

The stress–response is adaptive in the short-term, but it can be maladaptive if sustained levels of its mediators are chronically maintained. Furthermore, not all individuals exposed to chronic stress will progress to disease. Thus, understanding the causes of individual differences and the consequences of variation in vulnerability is of major importance. The aim of this review is to shed light on this issue by presenting a new naturalistic model of chronic psychosocial stress in male mice. Resident/intruder pairs of mice lived in continuous sensory contact and physically interacted daily. Four categories were identified: Resident Dominant, Resident Subordinate (RS), Intruder Dominant, and Intruder Subordinate. Behavior, autonomic and immune functions, hypothalamic–pituitary–adrenocortical responses, brain cytokine expression and cardiac histology were investigated in stress-exposed mice. Certain stress-induced alterations were present in all mice independent of their social status, while others clearly differentiated dominants from subordinates. RS mice showed a unique profile of alterations suggesting that the loss of relevant resources, such as the territory, is the key factor determining why only certain stress-exposed individuals ultimately show malignancy and psychopathologies.

Keywords: Allostasis; Allostatic load; Animal models; Autonomic function; Body weight; Cytokines; Corticosterone; Dominance; HPA axis; Immune functions; Loss of resources; Subordination

Contents

* Corresponding author. Present address: Istituto di Neuroscienze, Sezione di Psicobiologia e Psicofarmacologia, CNR. V.le Marx 15/43, 00137 Roma. Tel.: +39 06 8609 0252; fax: +39 06 827 873.
E-mail address: bartolomucci@biol.unipr.it (A. Bartolomucci).

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doi:10.1016/j.neubiorev.2004.06.009

"[…] war hysteria increases in intensity as one rises in the social scale."
George Orwell, *1984*.

"So ushered in the reign of Saul […] Saul made his decision, lunched himself […] but Menasseh got in a lucky shot from behind […] He was never in another fight, never mated again, disappeared to the bottom of the hierarchy. And he returned from whence he came, back to the wilderness."
Robert M. Sapolsky, A primate's memoire.

Social stress is a recurring factor in the lives of virtually all vertebrate species, and by virtue of its widespread occurrence, social factors are a key stimulus for the evolution of stress mechanisms [1]. Exposure to chronic social stress has been associated with many systemic and mental disorders. However, being exposed to social stress does not automatically predict subsequent pathological consequences, i.e. not all individuals exposed to social stress will progress to disease. Thus, determining the relationships between social factors and individual vulnerability to chronic social stress exposure has been recognized as a fruitful approach to shed light on the factors determining individual disease susceptibility [2–4] and will be the focus of this review.

1. The stress–response

The prototypical stress–response which has recently been re-conceptualized within the framework of allostasis and allostatic load, is today well understood [1,5,6]. There are two major systems mediating most components of the stress response. The first is the hypothalamic–pituitary–adrenocortical (HPA) system, which stimulates the adrenal cortex to release glucocorticoids such as cortisol or corticosterone into the blood. The second is the sympathico-adrenomedullary system that influences the stress–response through two different pathways working in parallel. One pathway is built up by the nerve endings that trigger the release of adrenaline from the chromaffin cells in adrenal medulla into the blood. The other pathway comprises the sympathetic nerve endings that innervate essentially every organ in the body [1,7,8]. The acute response, which the organism produces when challenged by an external and/or internal stimulus, is functionally implicated in the mobilization of energy needed for the behavioral response, and is adaptive in many ways. A recent example comes from the investigation conducted by Dhabhar and McEwen [9]. During a stress–response, several hormones and neurotransmitters allow an organism to mobilize all its resources to cope with the challenge. One of the effects at the immune level is that the immune cells moves from the 'barracks' (e.g. the spleen) to the 'battle stations' (e.g. blood, lymph nodes, skin) where they exert their function. In the Dhabhar and McEwen's studies, a cell-mediated immune response called delayed-type hypersensivity (DTH) was assessed. If the DTH was preceded by a session of restraint-stress, the result is a potentiation of the immune response [9]. This finding is in support of the adaptiveness of the acute stress response-the skin is one of the main route of access to the body for a pathogen for instance after a fight-induced injury. However, the problem with the stress response is that it is adaptive in the short-term but it can become highly maladaptive in the long-term. A classical example derives from the observation that a chronic elevation of glucocorticoids can induce a remodeling of the hippocampus, which has been implicated in the development of several psychopathologies [10–12]. Coming back to the studies of Dhabhar and McEwen, the immune response that was stimulated by the acute stress event was, on the contrary, depressed after an intermittent repetition of restraint-stress sessions over time, resulting in a reduced DTH response [9].

Thus, exposure to chronic stress has been found to be detrimental to health. This progressive change in physiology, due to prolonged or repetitive stress, has been recently termed allostatic load or alostatic overload [6]. Several recent

studies support the notion that an allostatic overload is more likely to develop when *unpredictable* stressors of *social nature, chronically* induce physiological and behavioral adjustments that may 'wear and tear' the underlying physiological functions [2,13]. For example, Koolhaas and coworkers reported higher and more prolonged corticosterone, adrenaline and heart rate increase following defeat from an aggressive conspecific as compared with traditional psychological and physical stress models [2,14]. In other words, negative social relationships seem to be a more potent source of chronic stress and disease. A possible explanation at a theoretical level lies in the observation that sociality is one of the most widespread phenomena in the animal kingdom. Living in a group, as any other behavioral trait, has costs and benefits, and because resources are not infinite in even the richest of ecosystems, access to such resources, and to mates is not distributed evenly among individuals belonging to a social group, i.e. individuals are generally not all equal [1,15]. Genetic, experiential and environmental factors will interact to determine the position of an individual within a dominance hierarchy [16]. Therefore, it is reasonable to assume that the hierarchical position in a rank will influence the way an individual copes with social and environmental challenges.

2. Stress and the social environment

Already in the seminal work of James Henry and coworkers it was evident that dominant male mice were more active, and responded to social interactions with predominantly a sympathetic adrenal-medullary pattern [3]. Subordinate males were less active and predominantly responded with a pituitary adreno-cortical pattern. In addition, after 9–10 months of grouping about one-half of the males had died. Interestingly, these deaths could not be attributed to fatal injuries, but appeared to be due to hypertension, cardiovascular damage and renal deterioration. In particular, blood pressure in males remained chronically increased even 9 months after the social phase ended, and the mice were now housed in isolation [3,17]. Moving from rodents to primates, Robert Sapolsky provided compelling evidences of stress-related disorders and the role of individual differences in a wild population of olive baboons [18–20]. Basal circulating levels of cortisol were lower in high-ranking individuals than in subordinates. The high cortisol level showed by subordinates was due to a hyper-production of hypothalamic corticotropin releasing factor (CRF) and a dampening of the HPA-axis regulatory feedback. Several subtle effects of social context emerged from the Sapolsky's investigations. First of all, it was clear that being dominant or subordinate in unstable circumstances is much worst than in stable conditions. A cortisol level in dominants and subordinates was increased in an unstable context. Second, unstable interactions with animals just below in the hierarchy induced marked hypercortisolism, while more unstable interactions with animals above in the hierarchy did not. This means that the potential risk of loosing the rank in the hierarchy is inherently stressful, while gaining is not. Again, this is not always the case, because a highly aggressive individual entering the group and gaining positions with continuous fighting had the highest cortisol level and the lowest lymphocyte counts.

These two examples, selected among the many available in artificial and natural environments [21–25], allow for a clear conclusion: social factors are powerful modulators of the stress–response and more importantly, they are so because they are real life events. These studies have inspired many other researchers to develop animal models of human psychopatholgies, which are based on stressful aspects of social stimuli [26]. For example, the Visible Burrow System (VBS), developed by Robert and Caroline Blanchard, enable groups of rat to engage in natural, stress-engendering, social interactions that constitute a particularly relevant model for investigating the behavioral, neural, and endocrine correlates of chronic stress, particularly when the focus is on individual differences [27,28]. Another example of an effective social stress model is the chronic psychosocial stress model developed in tree shrews by Eberhard Fuchs [12,29]. The results collected prove a strong face validity of the experimental procedure as a reliable model for major depression in humans [29]. In addition predictive validity was confirmed in a series of well-controlled studies. One of the first reports was a reversal of stress-induced behavioral and hormonal changes by the tricyclic antidepressant clomipramine [30]. In a more recent investigation, the atypic antidepressant tianeptine counteracted the stress-induced decrease of neurogenesis in the dentate gyrus and of level of neural brain markers in the hippocampus [31]. Finally, other drugs exerted effects similar to those of tianeptine [32], while the anxiolytic drug diazepam did not reveal a beneficial effect to any of the parameters studied supporting the view that in male tree shrews the state induced by psychosocial stress might be related more to depression than anxiety [33].

3. The (mis)fortunes of individuality

Beside the prominent role of negative social relationships as a source of stress, a common theme of almost all the above described studies is that 'although everyone encounters stress, not everyone proceeds to allostatic load to the same degree' [34, p.134]. Defeated, but not winner, tree shrews develop a depression-like state, while restraint-stress-responder and -non-responder subordinate rats in the VBS differ in various ways [12,35]. In other words 'bodies and psyches differ tremendously in their vulnerability to stress' [19, p.261]. Understanding the causes of these individual differences and their consequences in the terms of fitness, adaptive capacity and individual vulnerability to diseases is certainly one of the major challenges of modern biomedical

research. In the scientific and biomedical literature, individual differences are investigated at very different levels [19,36,37]: (i) the first level is investigated by correlating two or more parameters obtained from the same individual; (ii) a second level by grouping individuals on the basis of pre-screening in conventional behavioral tests (meant to determine genetic predisposition, i.e. an individual trait), or a different genetic background (see also Groothuis et al., Korte et al., and Sgoifo et al., in this issue); (iii) the last level (which is the one considered in the series of experimental data described below) by grouping individuals into classes which are identified on the base of state-like characteristics (i.e. the context in which a trait is expressed), such as dominants vs. subordinates, or on the basis of particular life events (see also Maestripieri in this issue).

The aims of this review is to present our model of chronic psychosocial stress in mice, summarize the results obtained in a number of experiments and conclude with a comprehensive discussion on the factors that may determine why certain individuals develop systemic or mental disorders when exposed to chronic social stress.

4. A mouse model of chronic psychosocial stress

We recently proposed an ethologically oriented model of chronic psychosocial stress, which is based on a natural behavior of male mice, i.e. acquiring and defending a territory [38]. In this paradigm, resident/intruder dyads live chronically in sensory contact and physically interact on a daily basis. The standard protocol (see Fig. 1), was adapted from ones developed previously with tree shrews and mice [30,39], and involves the use of resident adult male mice. These animals were individually housed for one week to allow for the establishment of an individual territory. Each resident mouse receives an intruder mouse (coming from group housing) and the two animals are allowed to interact freely for 10 min. After the interaction, the two animals are separated by means of a perforated polystyrene-metal partition, which allows continuous sensory contact but no physical interaction. The partition bisects the cages diagonally in two symmetrical compartments. The partition is then removed daily (for a total of 21 days) at an unpredictable moment between 09:00 and 12:00 h, i.e. in the

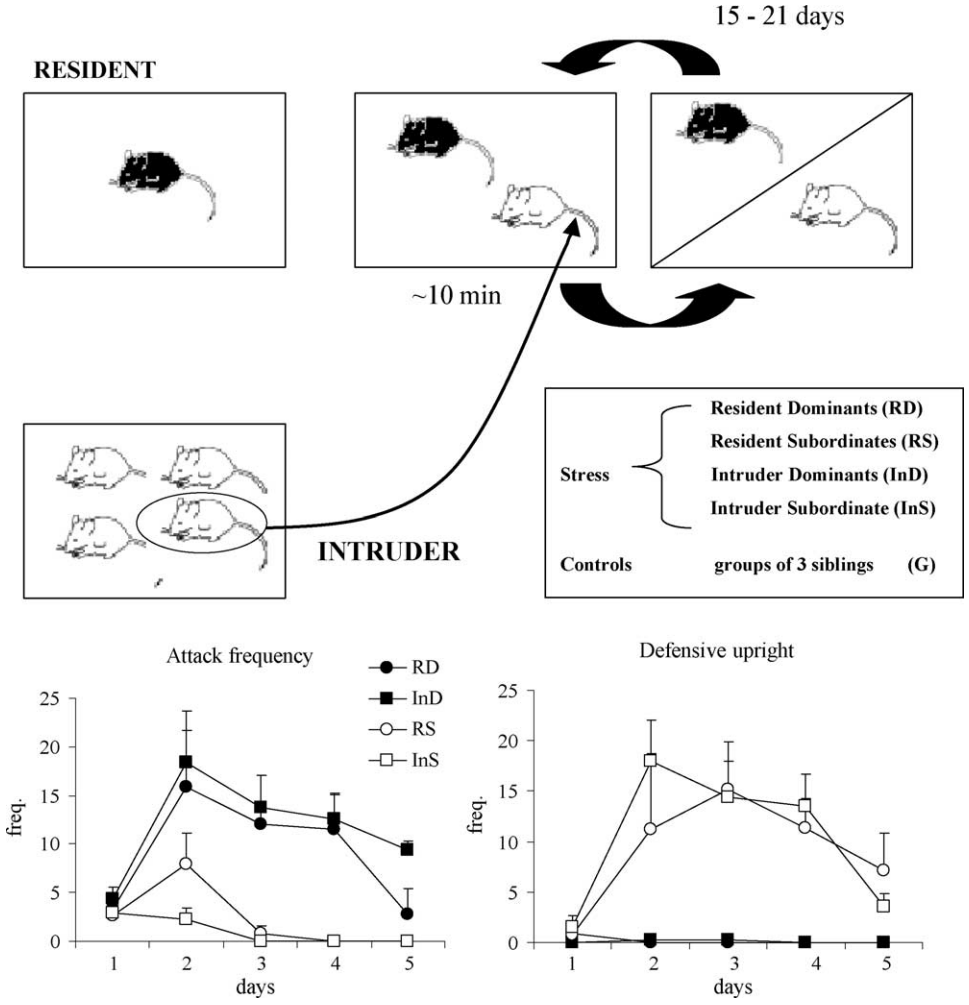

Fig. 1. A schematic diagram (upper panel) of the model of chronic psychosocial stress. Lower panel, behavior during the daily agonistic encounters. Data are presented as mean and SEM. Reprinted with modifications from [41].

initial part of the light phase. In the beginning of the stress protocol, the social relations between the resident and the intruder mouse undergo dynamic changes, which then lead either the resident or the intruder to acquire the dominant social rank. Accordingly, individual animals subjected to this procedure of social stress can be divided in four behavioral categories named: Resident Dominant (RD), Resident Subordinate (RS), Intruder Dominant (InD) and Intruder Subordinate (InS). Based on previous observations, showing that there weren't immune-endocrine or behavioral signs of stress in group-housed siblings, our controls (G) are 3 sibling male mice in a group-housed condition [38]. These animals are re-housed in groups of 3 (from pre-existing groups of 4–7 animals) on the same day when the chronic stress procedure starts and receive the same handling as the experimental animals.

Therefore, our model offers the opportunity to investigate whether territory ownership (being resident in a territory) and social status (being dominant or subordinate), as well as their interaction (e.g. a resident becoming dominant or subordinate) are factors affecting the individual vulnerability to stress exposure. In this model, the physical component of the stress protocol is of minor relevance when compared to the psychological one, because it is reduced to a brief daily physical interaction that is interrupted as soon as fight escalates in order to prevent injuries. Therefore, the effects we observed at the physiological and behavioral level are much more likely due to the psychological perception the mice have of the stressful context, i.e. pure psychological stress-induced effects.

Up to now, 192 (96 dyads) mice have been tested in our model of chronic psychosocial stress and it is interesting to point out that the percentage of resident and intruder mice attaining a dominant status is remarkably similar: 53% RD, 47% InD (as well 47% RS and 53% InS). Thus, prior residence has no effects in the context of chronic sensory contact, contrary to the case of an acute resident/intruder test [40]. The definition of dominant and subordinate mice under stable conditions can be easily detected by direct observation, because in most cases a stable hierarchy develops within a few days. When we quantified the agonistic behavior displayed by the mice during the daily agonistic interactions we observed that after the second day, only dominant mice (RD and InD) displayed aggressive behaviors (Fig. 1) [41]. Similarly, only animals that become subordinate (RS and InS) displayed a submissive posture such as the defensive upright (Fig. 1) [41]. Interestingly, the second or third day of interaction (depending of the dyad) when the partition was removed, the hierarchy was already established without any sign of fight between the two animals, i.e. one showed aggressive behavior and the other subordinates. From this observation it can be argued that, at least in the present experimental context, the definition of the social status does not occur because an animal won a fighting, i.e. during an interaction, but more likely because of a sensorial communication during the time the animals spent separated by the wire-mesh partition. Additional interesting details emerged from the behavioral analysis: (i) the total duration of the confrontation did not differ between the two dyads type, i.e. RD/InS vs. InD/RS; (ii) the amount and the duration of attack behavior did not differed between RD and InD; (iii) the occurrence of defensive upright postures displayed by InS and RS closely parallels the occurrence of attacks by the dominants [41]. One result needs further comments: RS mice show higher frequency and duration of attack on day 2 as compared with InS mice (Fig. 1), indicating territory defense against the intruder. Following this event, the resident mouse eventually becomes subordinate and during subsequent interactions its behavior does not differ from the behavior of intruders becoming subordinates.

A schematic outline of the results is presented in Table 1 and will be discussed further in the following sections (Behavior, HPA axis, etc.). Following this description, we will reconsider them in a comprehensive way to distinguish the primary elements underlying individual variability to stress exposure. This will be achieved by identifying the stress-induced alterations common to all behavioral categories (stress effects) from those in which dominant and subordinate clearly differ (status effect, comparing dominants and subordinates), and finally from the effects restricted to only one particular behavioral category (as it will be described below, RS mice).

5. Stress-induced behavioral alterations

Motor activity is the behavior most frequently studied in animal models of depression [12,42]. In other experimental paradigms, chronic social conflict induces a significant decrease in motor activity [12,13]. In the present study, subordinate animals (InS investigated at the moment) clearly showed reduced activity, while dominant animals (InD investigated at the moment) slightly increased their home cage motor activity as determined by radiotelemetry recordings (Fig. 2); [43]. Moreover, when chronically stressed mice were subsequently faced with a novel environment, by placing them in an open field, dominants (InD and RD), but not subordinates, showed consistent behavioral hyperactivity and reduced anxiety-like behaviors [38].

6. Stress-induced alterations of autonomic function

Chronic stress consistently induces hyperactivity of the autonomic nervous system [7]. By means of radiotelemetric techniques, we monitored InD and InS mice during the daily aggressive interactions and over the entire duration of the stress protocol [43]. In the acute response to daily aggressive interactions, InS showed a marked autonomic activation induced by the confrontation with their dominant counterparts (i.e. resident dominant) as indicated by the

Table 1
Summary of the effects of chronic psychosocial stress in mice

		Stress	RD	InD	RS	InS	Ref.
Behavior (activity)	Open field	=	+	+	=	=	[38]
	Home cage			=/+		–	[43]
General physiology	Body weight	–	–	––	++	+	[41]
	Food intake	=	=	=	=	=	
	Visceral fat	–	–	–	=	–	
	Spleen	=	=	=	=	+	
	Thymus	–	–	=	–	–	
	Preputials	+	+	+	=	=	
	Testis	=	=	=	=	=	
Autonomic function	Temperature	+?		++		+	[43]
	Heart rate	+?		+		+	
HPA axis	Corticosterone	+	+	+	+	+	[38]
	Cort after DST	+	+	+	+	+	[41]
	GR	–	–	–	–	–	[49]
	Adrenals	=	=	=	=	+	[41]
Immune functions	In vitro to ConA						
	Proliferation	=	=	=	–	=	[38]
	IL-2	=	=	=	–[a]	=	
	IFN-γ	=	=	=	=	=	
	IL-4	=	=	=	–	=	
	IL-10	=	=	=	–	=	
	In vitro to KLH						
	Proliferation	=	=	=	–	=	[66]
	IL-2	–	=	–	–	=	
	IFN-γ	=	=	=	=	+	
	IL-4	–	=	=	=	–	
	IL-10	=	=	=	=	+	
	Anti-KLH-IgM	=	=	=	=	=	[66]
	Anti-KLH-IgG	–	–	–	–	=	
	β-endorphine	=	=	=	=	=	[38]
Central cytokines	IL-1β	–	–	–	–	–	[49]
	IL-1Ra	–	–	–	–	–	
	IL-6	=	=	=	=	=	
	IL-10	=	=	=	=	=	
	TNF-α	–	–	–	–	–	
Cardiac histology	Fibrotic foci in left ventricular wall					+	[44]

[a] RS vs. InD. = − and + are expressed as compared to controls. ++ and −− have to be considered in relative terms within a specific function (a line). ? represent likely but not experimentally verified effects because two groups have not yet been investigated. Stress, all animals under stress procedure; RD, Resident Dominant; InD, Intruder Dominant; RS, Resident Subordinate; InS, Intruder Subordinate; HPA, Hypothalamus–Pituitary–Adrenocortical; DST, Dexamethasone suppression test; GR, Glucocorticoid receptor; ConA, Concavaline A; KLH, Keyhole limpet emocyanine; IL, Interleukin; IL-1Ra, Interleukin-1 receptor antagonist; IFN, Interferon; TNF, Tumor necrosis factor.

strong increase in both heart rate (HR) and body temperature (T) as compared to pre-interaction levels. A partial habituation was found for all parameters measured. A time domain analysis of heart rate variability in InS mice showed habituation of acute cardiac autonomic responsivity, i.e. the shift of sympathovagal balance towards sympathetic dominance was significantly less pronounced across repeated defeat episodes [44]. On the other hand, InD responded to the daily physical interaction (with resident subordinate mice) with marked tachycardia and hyperthermia without any sign of habituation over sessions. Therefore, despite subordinates showed a partial habituation of their cardiac responses, both dominant and subordinate mice continued to show marked autonomic activation over 15 days of repeated aggressive encounters and continuous sensory contact with the same mouse.

In the long-term, InD and InS mice responded to the stress procedure with a strong increase in heart rate and temperature, which was also affected by social status (Fig. 2). On the first day, HR and T increased dramatically above the pre-stress level. Following the very first day, both dominants and subordinates showed a strong tachycardia that lasted for about 6 days, and was evident during both the light/inactive and the dark/active phase of the daily cycle. At that point, differences between dominants and

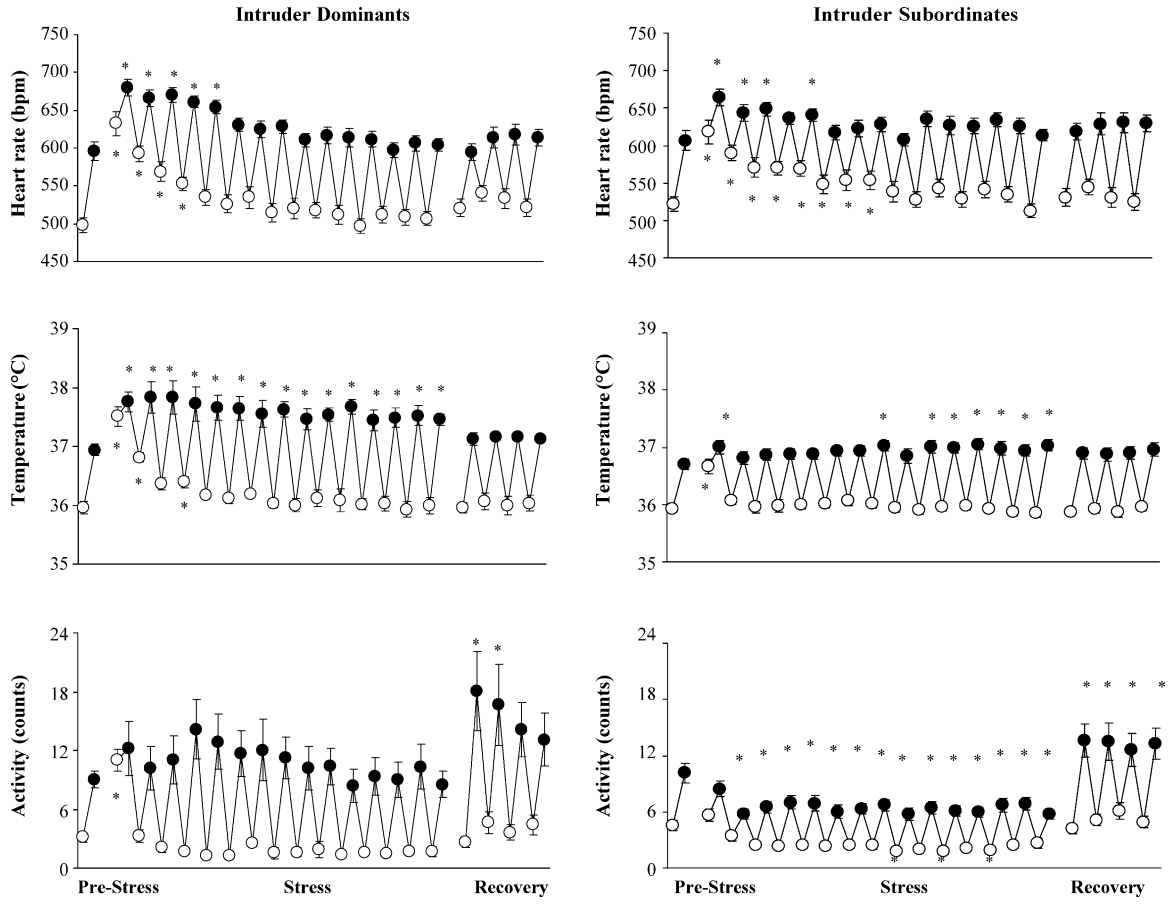

Fig. 2. Long-term changes in Heart Rate, Temperature and Activity values measured during the dark (filled circles) and the light (empty circles) phases of the daily cycle in Intruder Dominants and Intruder Subordinates. Values are presented for Pre-Stress, Stress and Recovery. $*p < 0.05$ compared to Pre-Stress corresponding value. Reprinted with modification from [43].

subordinates became more evident. Dominants maintained a strong dark phase hyperthermia for the whole stress phase, while subordinates showed a much smaller dark phase hyperthermia that appeared only some days later (8 days after stress onset).

One of the main features of 'The concept of allostasis' [6] is the dissociation between allostasis and allostatic load. While allostasis, i.e. maintaining stability through change, is regarded as a fundamental process through which organisms actively adjust to both predictable and unpredictable events, allostatic load (or allostatic overload) can be seen as the cumulative cost to the body in which serious pathophysiology can occur [6,10]. Our data clearly support the distinction since the HR and T rise measured during the daily aggressive interactions (allostatic state) did not correlate with long-term changes (resembling allostatic load) in the same parameters [43].

7. Stress-induced alterations of hypothalamic–pituitary–adrenocortical axis

In addition to the sympathetic response, activation of the HPA axis represents the hallmark of the stress–response and it has been repeatedly shown that chronic stress results in chronically elevated circulating adrenocorticotrophic hormone (ACTH) and glucocorticoids, and dysregulation of the HPA axis regulatory feedback [1,11]. In particular, it is possible to investigate the inhibitory feedback by means of the pharmacological test known as the dexamethasone suppression test (DST), which is based on the ability of dexamethasone (DEX) to inhibit the release of the endogenous cortisol or corticosterone [45,46]. Dysregulation of the HPA axis and resistance to DST are among the most consistent findings in depressed patient [46,47]. A similar profile also emerged in both subordinate baboons and rats under chronic stress [18,48]. Similarly, mice respond to our stress protocol by developing a higher basal plasma corticosterone level (measured in the nadir of the circadian fluctuation of this hormone, i.e. 2–3 h after light onset) when compared to controls [38]. This result was confirmed again in a more recent study [49]. Furthermore, stressed mice were subjected to the DST, and 6 h after DEX administration they showed resistance to the inhibitory effects of the DEX on the HPA axis, i.e. their plasma corticosterone level was 3 times higher than control mice [41]. In addition, by using whole structure RT-PCR, a downregulation of the glucocorticoid receptors (GR) was

observed in the hippocampus, but not in the pituitary and the hypothalamus (Fig. 3) [49]. This observation suggests a reduction in the inhibitory feedback exerted by the hippocampus over the hypothalamic CRH-producing paraventricular nucleus (PVN) cells [50] and a consequent hyper-production of CRH resulting in hyperactivation of the HPA-axis. In conclusion, mice under chronic stress develop a clear adrenal hyperactivity, likely due to an altered inhibitory feedback of the corticosterone on the hippocampus, which would lead to increased hypothalamic release of CRH. Interestingly, HPA axis alterations (corticosterone level, GR and DST resistance) developed in all stressed animals independently of whether they were dominants, subordinates, residents or intruders. This finding may indicate that the HPA axis is sensitive to the stressful nature of the situation per se and less modulated by the individual differences in the appraisal of the situation, at least under the present experimental conditions.

8. Stress-induced alterations of organ physiology and metabolic parameters

The prototypical stress-induced alterations described by Selye over 70 years ago [51; see also 13] also included a decrease in body weight and fat content, while the thymus, became atrophic and the adrenals enlarged. Changes in the body and internal organ weight of mice in our model closely resemble these prototypical alterations (see column 'Stress' in Table 1). Importantly, however, this general description matches the data only if we include overall trends for all animals subjected to the stress protocol. Dramatic differences in the magnitude of the changes emerge when social status and territory ownership are considered, i.e. if we consider the four behavioral categories of RD, RS, InD and InS mice [41]. The main individual differences concern the changes in body weight, which is regulated by many behavioral and neuroendocrine processes, and subjected to a quasi-deterministic balance between input (food intake) and output (thermogenesis; locomotor activity) [52]. Body weight changes were clearly modulated by social status. Dominants lost weight, while subordinates (particularly RS mice) gained significantly more weight than control mice. Food intake was unaffected by chronic stress exposure [41], thus input to the system cannot be the explanation for our findings. If food intake is maintained over time and body weight changes, then either overall metabolism or energy consumption must be affected in our mice. Interestingly, epididymal fat (the biggest reserve of visceral fat in mice) was lighter in all but RS mice when compared to controls. Dominant mice showed

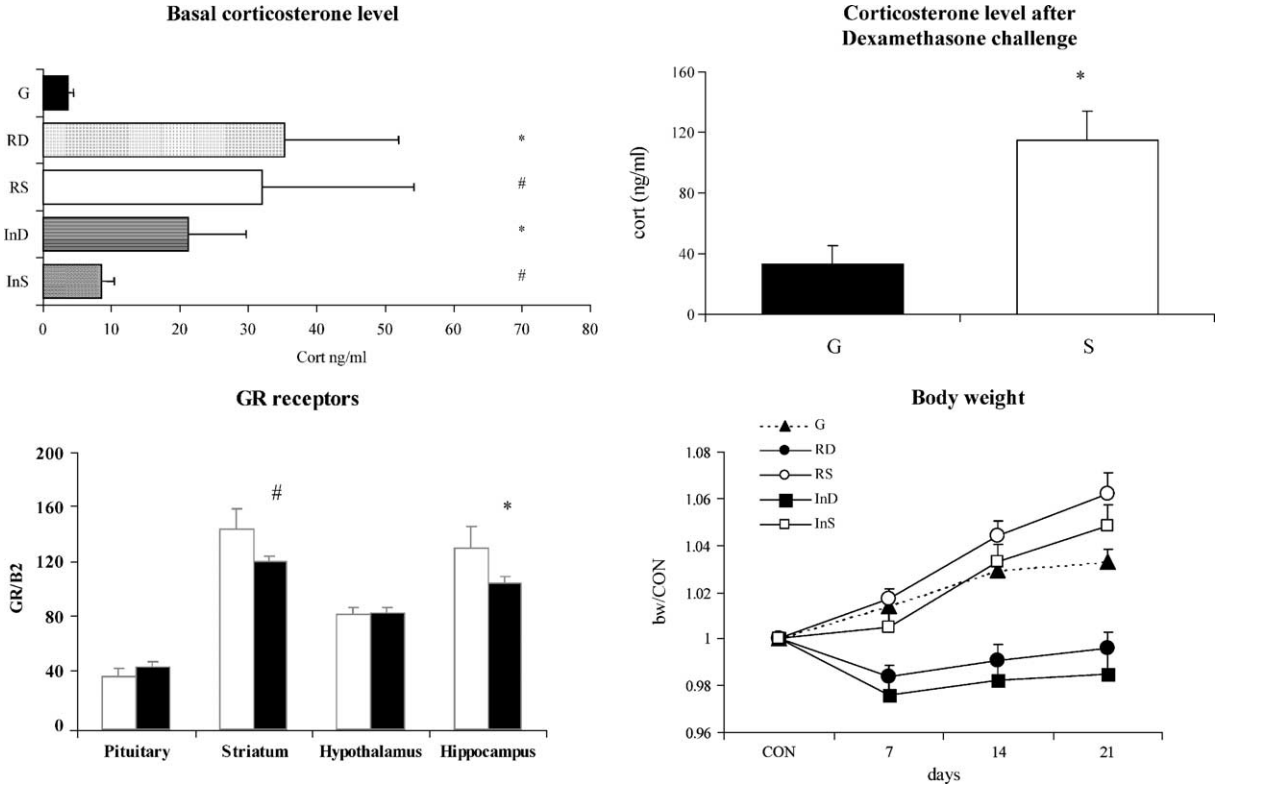

Fig. 3. HPA-axis parameters and body weight in mice under chronic psychosocial stress. Upper left, basal corticosterone level; *$p<0.01$ and #$p<0.05$ compared to G mice. Upper right, corticosterone level measure 6 h after 10 μg/100 g bw i.p. dexamethasone injection; *$p<0.05$. Lower left, GR level expressed as the ratio (%) of the radiolabeling incorporated in the specific PCR product to β2-microglobulin PCR product; *$p<0.05$; #$p<0.06$. Lower right, Body weight of control and stressed mice. Data are expressed as body weight at days 7, 14 and 21 relative to control body weight. Reprinted with modification from [38,41,49].

lower fat levels and decreased body weight, which may be ascribed to an activation of their HPA and sympathetic axis. Mechanisms involved in the chronic increase of autonomic functions observed under stress involves the hyper-activation of the HPA axis and the sympathetic nervous system [1,14] with central CRH playing a main HPA related and unrelated role [53]. This would be in agreement with our findings showing that dominant male mice have increased home cages activity and a marked activation of autonomic function and HPA axis [38,43]. Consistent with this hypothesis, mice over-expressing CRH showed a lower body weight than wild types [54]. On the other hand, in subordinate mice, we observed an increase in body weight, which was not associated with altered food intake (same input) while it was associated with a depression in home cage locomotor activity (lower output) [41,43]. However, in the present study, InS mice showed reduced fat weight while RS mice did not. This may reflect an alteration of the activity of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11-HSD-1), which converts the inactive 11-deydrocorticosterone to the active corticosterone, in RS mice. Indirect support to such a conclusion derives from the observation that mice over-expressing 11-HSD-1 only in their adipocytes do have an obese phenotype [55]. This hypothesis will explain the increased body weight observed in RS mice despite similarly high corticosterone levels existing in all animals exposed to chronic stress. Alternatively, the serotoninergic functions of RS mice, may be imbalanced since Bouwkenecht et al. [56] and Holmes et al. [57], recently reported a higher body weight for 5-HT_{1B} receptor and 5-HT transporter knock out mice, respectively, which is in agreement with the well know involvement of the serotonergic system in the regulation of aggression [58] as well as in feeding behavior [59].

9. Stress-induced alterations of immune functions

Along with neuroendocrine and behavioral alterations, social stressors can also have a strong impact on immune functions in both humans and other animal species [60–62]. In particular, when rodents are exposed to chronic (7 or more days) social defeat, it has been observed that there is a reduction in in vitro lymphocyte proliferation and natural killer cell activity as well as cytokine and antibody production [62–64]. In a first study we aimed at investigating the ex-vivo immune response of splenocytes to the T-cell mitogen Concavalin A (ConA) [37]. Splenocytes proliferation, as well as a panel of Type 1 (Interleukin (IL)-2 and Interferon-(IFN)-γ) and Type 2 (IL-4 and IL-10) cytokines, were analyzed. We found that only RS mice showed a decreased proliferation to ConA, while the production of Type 2 cytokines (IL-4 and IL-10), but not the Type 1 cytokines production was reduced (Fig. 4). Therefore, we noticed a decrease in Type 2 response and,

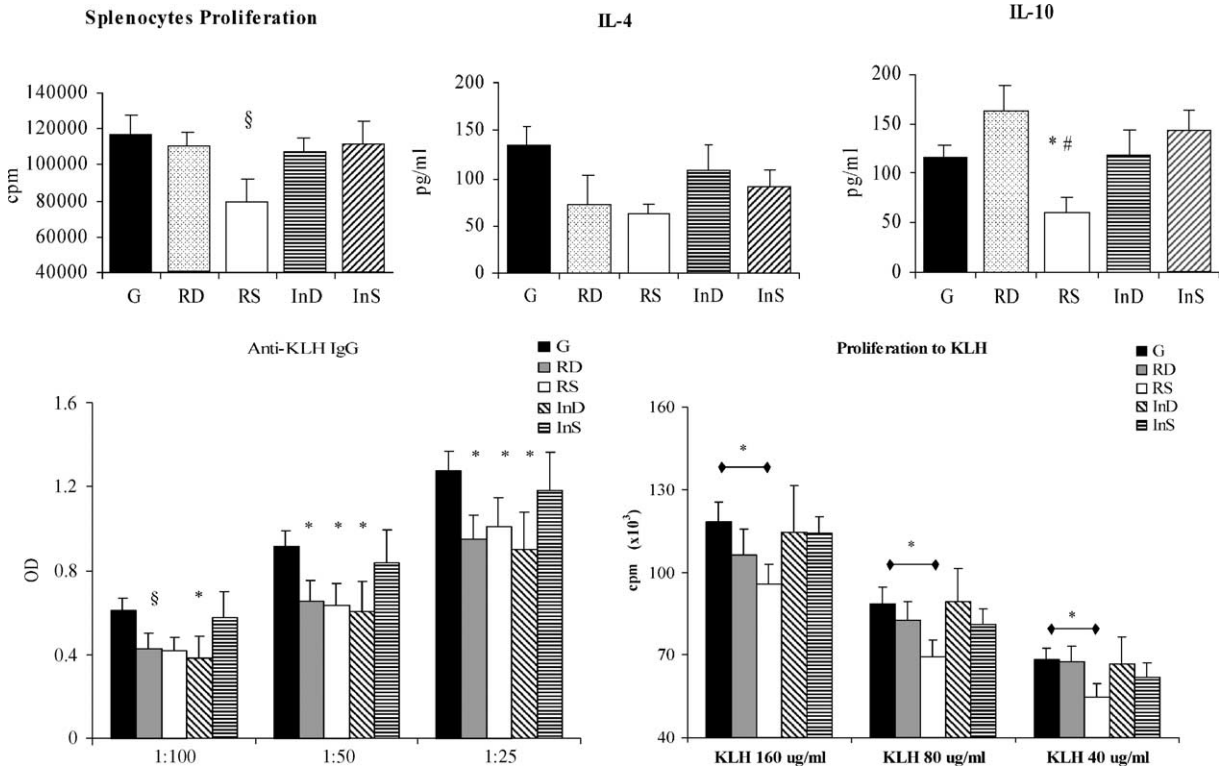

Fig. 4. Immune responses of mice under chronic psychosocial stress. Upper panels, Cytokines production (IL-4, IL-10) and splenocyte proliferation after in vitro ConA stimulation. *$p < 0.05$ compared to G, #$p < 0.05$ InD vs. RS, § $p = 0.051$ compared to G. Lower left, Anti-KLH-IgG; *$p < 0.05$ and §$p < 0.07$ vs. G mice. Lower right, in vitro splenocyte proliferation after KLH restimulation; *$p < 0.05$ vs. G mice. G = group housed siblings, RD = Resident Dominants; RS = Resident Subordinates; InD = Intruder Dominants; InS = Intruder Subordinates. Reprinted with modification from [38,66].

accordingly, a shift toward a Type 1 profile. Based on this evidence we would predict that RS mice should display reduced Th2 mediated functions, such as the production of antibody [65]. For this reason, mice were immunized with Keyhole Limpet Hemocyanine (KLH), seven days after stress-procedure onset [66]. Anti-KLH IgM and IgG were quantified 14 days after KLH immunization, with stress continuing trough. Furthermore, the splenocytes of KLH exposed mice were re-stimulated in vitro with KLH. Cell proliferation and production of cytokines IL-2, IL-4, IL-10 and IFN-γ were measured. As we expected, RS mice showed a decrease in anti-KLH IgG. In addition RS mice also had a reduced KLH induced proliferation in vitro and lower IL-2 release when compared to controls (Fig. 4). RS mice seem to show multiple immune impairments, i.e. antibody responses and cell proliferation. Results obtained in InS mice prove that subordination in itself is not the sole factor affecting the immune responses of RS mice [38,67]. Indeed, InS mice were the group showing neither a drop in IgG nor any other immune-impairment. Finally, RD and InD showed a lesser degree of immune change including the reduction of IgG. Corticosterone cannot be regarded as the only mediator of these effects [68,69] because plasma corticosterone was increased in all categories of animals (see above). It is possible that alterations in the level of other 'stress hormones' such as endorphins and cathecolamines might contribute to the results [70,71].

10. Stress-induced alterations of brain cytokines expression

Cytokines are potent, multifunctional, pleiotropic proteins that were initially characterized in the context of cellular activation and communication in the immune system. However, they are also present in several brain structures and produced by multiple cellular types, e.g. glia and neurons [72,73]. These molecules have the peculiarity of being produced and acting as a network, in the sense that several cytokines are produced in response to the same stimulus with intricate mutual relationships in their production and activity. A growing body of evidence also points to a possible still poorly defined role for the network of central cytokines in stress-related disorders, including depression [74–77]. However, a clear alteration of central cytokines under conditions of chronic stress has never been demonstrated [78]. Several brain areas (hippocampus, hypothalamus and striatum as well as the pituitary) of mice subjected to our stress model were analyzed for cytokine [Interleukin (IL)-1β, IL-6, IL-10, IL-1Receptor antagonist (Ra), Tumor Necrosis Factor (TNF)-α)] expression at the mRNA level by semi-quantitative RT-PCR [49]. Stressed mice showed decreased levels of transcripts for IL-1β in the hippocampus, IL-1Ra in the striatum and pituitary, and TNF-α in the striatum and hippocampus as compared to control mice. The results of the present study provide one of the first examples of a modulation of the cytokine network by chronic social stress, in the absence of any inflammatory stimulus, such as fighting injuries or LPS injection [79]. Glucocorticoids are the best candidate for such a down-regulation of cytokine transcripts in the brain [80–82]. Accordingly, as it was for the glucorticoids levels (see above), also central cytokines are similarly affected in all mice under stress. Based on present knowledge on the role of central cytokines, these findings may open new perspectives for understanding the pathophysiological basis of chronic stress-induced disorders [74,75].

11. Stress-induced alterations of myocardial structure in InS mice

A link between stress and altered cardiovascular function has been demonstrated repeatedly [14]. Myocardial damage, one of the major risk factors for heart failure [83], has been found as well in animal models of social stress [84]. Therefore, we investigated whether mice under our chronic stress model would show alterations in the myocardial structure [44] (the investigation up to now has been conducted only in InS mice). We were able to show that the volume fraction of fibrosis in the left ventricular wall was 6-fold larger in InS than in control animals due to a significantly higher number of fibrotic foci. These results show that chronic psychosocial stress can induce cardiac structural changes and allows one to hypothesize that a psychosocial challenge of longer duration might produce more severe structural damages, predisposing to a susceptibility to arrhythmias [83].

12. Conclusion: social factors determine individual vulnerability to chronic stress exposure

Not all individuals are equal and this is a key element for the action of natural selection [85,86], but as already discussed, individuality can be sometimes a misfortune when considered in terms of pathology development. In Table 1 we summarize the findings obtained in our chronic stress paradigm. The table has two main sections, one describing the effect of the protocol per se on all the animals collectively (labeled Stress). This reflects to evaluating weather living under a continuous stress, in behavioral term, might or not affects mice behavior and physiology. The second part of the Table 1 describes the source of variability we investigated. When considering the column 'stress', the picture almost closely matches the classical picture observed in many animal models of chronic stress [1,13, 25,26] specifically: body weight decreases; the thymus is reduced; animals lose fat mass; they show higher heart rate and hyperthermia; the HPA axis is hyper-activated resulting in high circulating corticosterone, escape from the

suppressive effect of dexamethasone and reduced glucocorticoid receptor levels; central cytokines mRNA are down-regulated. Importantly, the stress-induced changes in autonomic function, HPA and central cytokine activity are common to all animals regardless of being dominant, subordinate, resident or intruder. This generalized effect suggests these systems are more sensitive to the stressful situation per se and less modulated by the individual appraisal of the situation, at least under the present experimental conditions. When evaluating the validity of our model it is critique to evaluate if, after 21 days of chronic stress, animals are still dynamically adapting to the stressful context or if they reached an adaptive balance/maladaptive unbalance. The answer appears to critically depend on the physiological function considered. For example, body weight appears to be still under dynamic change (Fig. 3), while heart rate clearly adapted after 6 days of chronic hyper activation (Fig. 2). It must be noted, however, that most of the endocrine and immune functions have been determined at the end of the experiment and in un-stimulated conditions (animal killed while resting in the home cage, and 24 h after the last fight) and thus the alterations observed are not, probably, part of an adaptive response to acute fight, but more likely part of an adaptive/maladaptive adjustment (to evaluate if the alterations observed are, or not, at the apex of their alterations would require further studies). Finally, endocrine disregulation in the DST and cardiac fibrosis may probably be considered as long-term or permanent alterations. In conclusion, more studies are needed but our model can be considered as a valid model of chronic stress [26–29].

Examination of the remaining four columns of the Table 1 reveals a number of differences between dominants and subordinates. RD/InD differ from RS/InS: body weight decreased in the dominants and increased in the subordinates; dominants are hyperactive in both home cage and a novel environment; subordinates show a dramatic drop of locomotor activity in the home cage; dominants show a very strong hyperthermia during their active phase. Social status is one of the key factors modulating individual variability and this is true for a great variety of animal species [22,25 for reviews]. In addition to this general remarks, our results support one of the more classical observations in the stress field: dominants tend to have a more hyperactive autonomic nervous system (in some case also in association with higher HPA axis) than subordinates [17,22]. Thus, it is tempting to suggest that our experimental procedure elicited two different profiles depending on the social status of the subject. Namely, dominants seem to develop a hyperactive autonomic nervous system in association with behavioral activation and attempt at coping, while subordinates evidenced a state resembling sickness behavior, giving up and helplessness.

Interestingly, the behavioral and physiological alterations of Resident and Intruder Dominants are remarkably similar (cfr. Table 1). Evidences are accumulating for a physiological ‘cost of being dominant’. When compared with subordinates, dominants showed higher stress-markers in many cooperative and non-cooperative breeding species [22,87]. In contrast with data obtained in the field, however, relatively few laboratory investigations report higher stress induced alterations in dominants respect to subordinates or controls, in part because dominants are less investigated and much of the emphasis is on defeated/subordinate individuals [13,17,88]. What clearly emerges in the wild, however, is that dominance (and the same is true for subordination as will be discussed below) is not negative in itself, but it might be so depending on the social context in which the status is acquired and maintained, and on the relative stability of the hierarchy [19,67,87]. It is important here to make a distinction between studies where a dominance/subordination relationship is used as a model of chronic stress (the majority of laboratory studies), and studies in the field or under stable and semi-naturalistic conditions. In the field and semi-naturalistic contexts, dominance may have costs but is certainly also associated with priority of access to resources and several other social and non-social benefits. Dominance is, in other words, a behavioral strategy regulated by cost/benefit equations depending on the inherited specie-specific social organization and on actual environmental and social conditions [15,16,86,87]. In social stress based laboratory models, instead, dominants rarely have benefits (no prior access to resources) so the context where dominance is attained is probably not so important. In addition, dominants may have no costs associated with having that rank while often they may have a negative balance. Almost all models of social stress, in fact, work because researchers take advantage of the inherited predisposition of high rank/dominant/resident individuals to aggressively exclude potential same-sex competitors, thus having a high level of energy expenditure and an overactive SNS. In the house mice, high levels of territoriality and intolerance against same-sex conspecifics characterize the males, and under natural situation it is unlikely that an unfamiliar mouse defeated by a dominant would remain into his territory [40,89]. In this connection, for a mouse to attain the dominant rank in our stress model has some physiological ‘costs’, as discussed above, and this appear to be poorly related to maintaining (RD) or to get (InD) a territory. The possible cause of this ‘costs’ could be the unnatural forced cohabitation that is imposed to a dominant and a subordinate. In addition, a dominant face the demanding situation of being unable to expel an intruder from his territory despite continuous hostility (reminiscent of the Orwellian’s *war hysteria*) while being also devoid of obvious benefits, thus explaining the homogeneity between RD and InD.

While the behavioral and physiological changes of RD and InD are similar, the same conclusion isn’t true for resident and intruder subordinates which clearly differ in many parameters (cfr. Table 1). The concept of ‘subordina-subordination stress’ has been theoretically formulated and experimentally validated in many species [90,91].

Subordination is usually regarded as the prototypical model of social stress [28]. However, it has already been suggested that physiological correlates of rank are also sensitive to the individual's experience of that rank, modulated by personality and sensitive to the social setting in which the rank occurs [19,67,87]. Our data confirm this view by showing that it is not subordination by itself that is detrimental to health even in laboratory conditions, and provide a possible explanation. From Table 1, it is clear that Resident Subordinates and Intruder Subordinates did not show similar profiles. RS mice showed a strong increase in body weight, while being the only category to show a strong depression of immune functions. On the contrary, InS mice show virtually no immune impairment and smaller weight changes. Anxiety and depression are associated with higher HPA-axis activation and there is often co-morbidity with obesity [92,93]. Obesity is also associated with immune impairment, the more replicated findings being a reduced mitogen-induced lymphocytes proliferation [94]. These observations may create a link between individual variability in immune responses and the body weight changes we observed. In fact, Resident Subordinates showed a reduced proliferation to ConA and to KLH, as well as a consistent gain in body weight. That the immune system is strongly affected is of main interest. Having impaired immune system functions may predispose the organism to a number of pathological conditions, ranging from infection to cancer.

Why should Resident and Intruder Subordinates mice differ? When considering the behavior during the daily agonistic interaction, apparently no difference appears between RS and InS but one: RS are much more aggressive in the second day than InS [41]. Could this single difference in the second day out of 21 aggressive encounters explain the observed results? (This would resemble the long term-changes occurring in rats after a single or double social defeat [95,96]). Probably not, as we have already argued [41], while we would like to suggest that this behavioral difference might underlie a different motivation between RS and InS, i.e. residents but not intruders defend their territory. In fact, what occurs in the first days of the procedure is that an intruder who entered in his territory and become dominant defeated a resident mouse, owner of a territory. Indeed this is the only difference existing between a resident and an intruder mouse becoming subordinates. Thus, losing a territory (a resource for a male house mouse) appears to be a more likely explanation for the differences emerging between RS and InS mice. Some evidence collected in rodents and primate species seems to support our conclusion: dominant mice losing their rank develop hypercortisolemia [17]; outcast males, which are rats loosing the dominant rank, in experimental colonies develop serious pathologies [97]; dominant rats becoming subordinate develop depression-like disorders [98]; for a male olive baboon, being challenged by a lower ranking animal has more serious consequences in terms of stress response than being aggressed by higher rank ones [20]. Thus, our observation seems to be in keeping with findings in other social mammals: losing a resource (dominance status or a territory) is a dramatic event, which may lead to a prolonged change in physiology (an allostatic load), which may lead to the development of pathology due to allostatic overload [6].

As an emblematic example of such an effect, it can be taken the description Sapolsky provide of the life history of 'the king' Saul presented in the incipit of this paper. If this interpretation is correct, then the aim of future research should be to elucidate the nature of the most relevant resources for a given species. This knowledge should help understanding observed differences in response to different models of stress, in different species and between sexes. This knowledge would also help us to predict individual variation in vulnerability to the development of diseases under stressful conditions.

A final issue needs to be addressed concerning the relevance of our conclusions to human beings. Can loss of resources and hierarchical position be important for humans too? Specifically, can resource loss be a factor related to the development of pathology? It seems widely accepted that the socio-economic status makes a difference, the lower the status, the higher the risk to develop a plethora of pathologies [99] (Interestingly the effect of socio-economic status remains substantially unchanged even after correcting for many factors such as health-care, education and health-promoting life style factors [100]). However, concepts from animal research such as territoriality and social hierarchy may help to inform us about the human condition and the development of both physical and psychological pathologies. Indeed, in a recent paper, Peter Rhode directly addressed these questions [101]. First, the author answers that hierarchical and territorial behaviors are widespread in humans. Then, he proposes a new perspective on depression, called '*The social competition hypothesis of depression*' [102]: 'the hypothesis also predict that depression is linked to hierarchical defeat in humans' [101; p. 222]. Therefore, loss of hierarchical position and resources, as well as conflict of internal hierarchical aims seem to be crucial factors determining the physiological alterations associated with depressed mood and even clinical signs of depression [101,103].

Acknowledgements

Many colleagues from the Universities of Parma and Milan, and the Laboratoire de Neurobiologie Intégrative of Bordeaux, contributed to the studies described and we kindly acknowledge all of them, in particular: J. Arsaut, G. Ceresini, A. Chirieleison, T. Costoli, E. Merlot, P.J. Neveu, T. Pederzani, M.D. Poli, V. Vascelli. A special thank goes to E. Choleris, E. Fuchs, M. Kole and, especially, to R.M. Sapolsky who provided theoretical feedback and/or practical help over the years, which considerably contributed to the realization of the research described. M. Kavaliers

commented the final version of the manuscript. The title 'The misfortune of individuality' is a chapter head of R. Dantzer's *The psychosomatic delusion* (Free Press; 1993). Nothing would have been the same without the 'social support' of F.B. Supported by ASI.

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